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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,731	02/27/2004	Jason R. Fink	58210US004	6098

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EXAMINER	
HAMUD, FOZIA M	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
05/02/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/788,731	FINK ET AL.	
	Examiner	Art Unit	
	Fozia M. Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 7-56* is/are pending in the application.

4a) Of the above claim(s) *7,8,23,24 and 35-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9-34 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Applicant's Amendment:

1a. Applicants' amendment filed on 29 January 2007 has been entered.

Status of Claims

1b. Claims 4-6, have been cancelled, and new claim 56 has been added. Thus, claims 1-3, 7-56 are pending, of which claims 7-8, 23-24, 35-55 stand withdrawn for being drawn to a non-elected invention and claims 1-3, 9-22, 25-34 and 56 are under consideration in the instant application.

Specification:

2. Applicants' amendment to the specification correcting typographical errors and citing published U.S. Patent Publication numbers instead of U.S. Patent Application serial numbers is entered. No new matter is added to the specification.

Response to Applicant's Argument:

3. The following rejections are withdrawn in light of Applicant's arguments:

3a. All of the rejections of cancelled claims are moot.

3b. The rejection made against claims 1-6 and 25-34 as being anticipated by Hemmi et al (January 2002) is withdrawn, because the amended claims recite the use of human cells that naturally express TLR7 and TLR8, however, the Hemmi et al reference uses murine and human cells that do not naturally express TLRs.

3c. The rejection made against claims 1-6 as being anticipated by Jurk et al (June 2002) is withdrawn, because the amended claims recite the use of human cells that

naturally express TLR7, however, the Jurk et al reference uses artificial human cells that do not naturally express TLRs.

3d. The rejection of claims 1-6 made under 35 USC § 102(a) as being anticipated by Gibson et al. (Cellular Immunology, vol. 218 (2002), pp. 74-86), is also withdrawn, because Gibson et al do not teach performing an assay that detects TLR7-mediated cellular activity and an assay that detects modulation of a TLR8-mediated cellular activity, together as required by the instant claims. Gibson et al. teach an assay to detect TLR7 agonists that stimulates human plasmacytoid dendritic cells (pDC) to produce a number of cytokines including TNF-α, IP-10, interferon-α and interferon-ω. However, this reference does not teach the simultaneous use of two assays, one detecting modulation of TLR7 mediated cellular activity and the other detecting modulation of TLR8 mediated cellular activity, as encompassed by the amended claims.

Response to Applicants' Amendment:

Claim Rejections - 35 U.S.C. § 112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4a. The rejection of claims 1-6, 9-22 and 25-34 made under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained for reasons of record, set forth in the office action mailed on 29 September 2006.

Regarding claim 1, Applicants argue that the starting material, the endpoint and the expected result all depend on the particular assay chosen in the practice of the

invention. Applicants submit that the specification provides detailed description of one such assay, wherein Myeloid dendritic cells (mDCs) are activated by a TLR7/8 agonist and a TLR8-selective agonist, but are not activated by a TLR7-selective agonist, and Plasmaeytoid dendritic cells (pDCs), on the other hand, are activated by a TLRT/8 agonist and a TLRT8-selective agonist, but not a TLR7-selective agonist. Therefore, the selectivity of a test compound with respect to TLR7 and TLR8 can be determined by contacting the test compound with a population of mDCs and a separate population of pDCs, a test compound that activates mDCs but not pDCs is TLR8-selective; a test compound that activates pDCs but not mDCs is TLRT7-selective. Applicants further argue that their disclosure describes the assay to be used (activation of mDCs and pDCs), the starting material (mDCs, pDCs, and test compound), what to test for (CD80 expression by each population of cells), and what result to expect (test compound will activate one cell population and not the other).

These arguments have been fully considered, but are not deemed persuasive. Applicants are arguing limitations not recited in the claims. Although the claims now recite the use of human cells that naturally express either TLR7 or TLR8, the claims do not recite how to perform the assay or what activity or result to measure. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, the skilled artisan would not how to perform the claimed method.

Regarding claims 9-24, Applicants argue that those skilled in the art, armed with Applicants' disclosure and having knowledge of the expression of various TLRs among

populations of immune cells, can practice the method recited in claim 9. Applicants further submit that the disclosure defines "TLR modulation profile" as follows:

'The TLR modulation profile of a given compound refers to the observed profile of TLR mediated cellular activities modulated by the given compound. The observed profile may be compiled from a single source or multiple sources and may be derived from, for example, experimental assay results, clinical or anecdotal observations, or any other suitable source'.

Applicants also argue that one skilled in the art can identify the TLR modulation profile for any specific compound from the known TLR agonist properties of the compound, collected from any of the enumerated sources. That is, one skilled in the art can identify whether a compound is, for example, a TLR7 agonist or a TLR7/8 agonist.

These arguments have been considered, but are not deemed persuasive. It is acknowledged that the skilled artisan can identify whether a compound is an agonist or an antagonist of a particular toll like receptor, (TLR), and whether said compound modulates, i.e, stimulates or inhibits a cellular activity mediated by said TLR, from the known properties of the compound, however, claims 9-24 are unclear, because it is unclear what is being claimed. Are the claims drawn to a screening method, if so, what are the steps of the method? The way claims 9-24 are drafted, one skilled in the art would not know what are the positive steps of the claimed method. For example, suppose that the skilled artisan knows that a compound is a TLR2 agonist from the compound's known profile, and performs experiments that confirm that said compound is indeed an agonist of TLR2, then, what is the next step. Therefore, it is unclear what claims 9-24 add to the already known information about said compound. Accordingly,

no meaningful interpretation can be obtained for claims 9-24, because the disclosure does not describe or teach how to practice the method claimed therein.

With respect to claims 25-33, Applicants submit that claim 25 recites a method for selectively modulating cells of the immune system and that one skilled in the art, seeking to practice the invention, would approach the method with the starting cell populations in mind, for why else would that person want to selectively modulate the activity of the cells? One characteristic that a person skilled in the art can look for is TLR expression profile. Applicants further argue that the claim specifically recites that the selected compound modulates a TLR-mediated cellular activity of the first cell population to a different extent than it modulates a TLR-mediated cellular activity of the second cell population.

These arguments have been considered, but are not deemed persuasive. Claim 25 does not recite what to test for, how the compound that modulates TLR7 or TLR8 mediated cellular activity, or wether it stimulates or inhibits said activity. There are no steps to the method, all that is recited is human cells that naturally express TLR and a compound that modulates a cellular activity mediated by said TLR, but no recitation of which cellular activity, how to test said activity and what is the expected result.

Fozia, is there a use for selectively modulating cells of the immune system by activating either TLR7 or TLR8? If so, what is it? Could this be an enablement or utility issue?

New Rejections Necessitated by Applicants' Amendment:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5a. Claims 1-3, 25-34 and 56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound that selectively modulates a TLR7 mediated cellular activity or a method of identifying a compound that selectively modulates a TLR8 mediated cellular activity, said method comprising culturing specific cells and measuring the expression of specific cytokines or costimulatory proteins, and a method of selectively modulating specific immune cells that naturally express TLR7 or TLR8 by using an agonist for either TLR7 or TLR8 and measure the expression of specific cytokines or costimulatory proteins, does not reasonably provide enablement for a method of identifying a compound that selectively modulates at least one TLR-mediated cellular activity, the method comprising, providing "all possible" assays to detect modulation of a TLRT7 mediated cellular activity, and also providing "all possible" assays to detect modulation of a TLR8 mediated cellular activity, performing the two assays simultaneously by using the test compound and "all possible" human cells that naturally express either TLR7 or TLR8; and identifying the test compound as a compound that selectively modulates at least one TLR7 or TLR8 mediated cellular activity or a method of modulating "all possible" human cells that express TLR7 or TLR8 and contact them with an agonist of TLR7 or TLR8 and measuring an unknown cellular activity mediated by said TLR7 or TLR8. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, practice the invention commensurate in scope with these claims.

Claim 1 encompasses performing an assay for identifying a compound that selectively modulates a TLR7 mediated cellular activity together with an assay for identifying a compound that selectively modulates a TLR8 a mediated cellular activity, however, the specification teaches an assay using HEK293 cells transfected with a gene encoding either TLR7 or TLR8 and a NF-kB luciferase reporter plasmid, measuring NF-kB activation in said cells, (see example 1 and table 5). The specification also discloses an assay using Plasmaeytoid dendritic cells (pDCs), or Myeloid dendritic cells (mDCs) that are activated by either TLRT7 agonists and/or a TLRT8 selective agonists, and measuring the expression of CD80 costimulatory protein or IL-12, (see examples 3 and 4). Thus the specification provides assays which use specific cell lines and measure the activation of specific cellular activities or measure the expression of specific proteins, however, claims 1-3 encompass assays using "all possible human cells that naturally express TLR7 or TLR8 to detect modulation of "all possible" TLR7 or TLR8 mediated cellular activities, without identifying which activities to test for. Furthermore, claims 1-3 encompass performing an assay to detect modulation of a TLR7 mediated cellular activity and an assay to detect modulation of a TLR8 mediated cellular activity together, while the specification discloses performing each assay separately, (see examples 1-4).

Claims 25-33 and 56 encompass a method of identifying a first human immune cell population that naturally expresses TLR7 and a second human immune system cell

population that naturally expresses TLR8, and contacting said cells with a compound that either modulates TLR7 or TLR8 mediated cellular activity, however, the specification discloses that Plasmaeytoid dendritic cells (pDCs) and Myeloid dendritic cells (mDCs) which are activated by either TLRT7 selelctive agonists or TLRT8 selective agonists, respectively, and the TLR mediated cellular activities to measure are the expression of CD80 costimulatory protein or IL-12, thus these claims are only enabled with respect to using these cell lines and measuring these specific activities. The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant case, one skilled in the art would not be able to select a human cell line that naturally expresses either TLR7 or TLR8, from the infinite number of human cells that might naturally express TLR7 or TLR8 and would not know which of the infinite number of TLR7 or TLR8 mediated cellular activities to test for. Moreover to practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve selecting human cells that naturally express TLR7 or TLR8, identify which cellular activities might be mediated by

TLR7 or TLR8 and test for said desired activities. It is this additional characterization of the disclosed composition that is required in order to obtain the functional data needed to permit one to practice the claimed method coupled with the lack of direction/guidance presented in the specification regarding how to perform the recited assays, which constitutes undue experimentation for the skilled artisan to practice the claimed invention in its full scope.

New Matter Rejection:

5b. Claims 1 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1 and 25 recite "....human cells that naturally express TLR7" and " .... human cells that naturally express TLR8...", which introduces new matter into the claims, because, there is no support for these limitations in the specification as originally filed. Cells to be used in the claimed method are disclosed on page 9, lines 17-23, page 22, lines 20-30 and examples 3 and 4, however, nowhere on these pages or anywhere else, does the specification disclose that the cells to be used are "human cells that naturally express TLR7" or " .... human cells that naturally express TLR8...". Examples 3 and 4 disclose using Plasmaeytoid dendritic cells (pDCs), or Myeloid dendritic cells (mDCs), however, it is not disclosed that these cells are human cells, and even if they were, that is no support for 'human cells that naturally express TLR8 or TLR7".

Conclusion:

6. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M. Hamud whose telephone number is (571) 272-0884. The examiner can normally be reached on Monday, Thursday-Friday, 6:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fozia Hmaud
Patent Examiner
Art Unit 1647
25 April 2007

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER